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Evaluation of carbapenems for multi/extensive-drug resistant *Mycobacterium tuberculosis* treatment

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Abstract

M/XDR-TB has become an increasing threat in high burden countries but also in affluent regions due to increased international travel and globalization. Carbapenems are earmarked as potentially active drugs for the treatment of *M. tuberculosis*. To better understand the potential of carbapenems for the treatment of M/XDR-TB, the aim of this review was to evaluate the literature on currently available *in vitro*, *in vivo* and clinical data on carbapenems in the treatment of *M. tuberculosis* and detection of knowledge gaps, in order to target future research.

In February 2018, a systematic literature search of PubMed and Web of Science was performed. Overall the results of the studies identified in this review, which used a variety of carbapenem susceptibility tests on clinical and lab strains of *M. tuberculosis*, are consistent. *In vitro* the activity of carbapenems against *M. tuberculosis* is increased when used in combination with clavulanate, a BLaC inhibitor. However, clavulanate is not commercially available alone, and therefore is it practically impossible to prescribe carbapenems in combination with clavulanate at this time. Few *in vivo* studies have been performed, one prospective, two observational and seven retrospective clinical studies to assess effectiveness, safety and tolerability of three different carbapenems (imipenem, meropenem and ertapenem). Presently we found no clear evidence to select one particular carbapenem among the different candidate compounds, to design an effective M/XDR-TB regimen. Therefore more clinical evidence and dose optimization substantiated by hollow fiber infection studies are needed to support repurposing carbapenems for the treatment of M/XDR-TB.

47 **Introduction**

48 Treatment of tuberculosis (TB), a disease caused by *Mycobacterium tuberculosis*, has become more
49 challenging with the emergence of multidrug resistant (MDR)-TB and extensively drug resistant
50 (XDR)-TB among previously and newly detected cases **(1).** M/XDR-TB has become an increasing
51 threat in high burden countries but also in affluent regions due to increased international travel and
52 globalization.

53

54 MDR-TB is defined as an infectious disease caused by *M. tuberculosis* that is resistant to at least
55 isoniazid and rifampicin. XDR-TB is defined as MDR-TB with additional resistance to at least one of
56 the fluoroquinolones and to at least one of the injectable second line drugs (amikacin, capreomycin
57 or kanamycin). New TB drugs, with a novel mechanism of action, include bedaquiline and delamanid
58 that have recently been approved and included in the World Health Organization guidelines on MDR-
59 TB as add-on agents **(2).** Unfortunately resistance to these agents has already been detected **(3).**
60 Exploration of currently available drugs for their potential effect against TB, may be an additional
61 source for potential candidates to be used in case of extensive resistance to try to compose a
62 treatment regimen **(4-5).**

63

64 Beta-lactam antimicrobial drugs are widely used drugs for the treatment of a range of infections.
65 Also, imipenem-cilastatin and meropenem have been listed as add-on drugs in the updated WHO
66 treatment guidelines **(6).** Carbapenem activity has long been considered to be of limited use, due to
67 rapid hydrolysis of the beta -lactam ring by broad-spectrum mycobacterial class A beta-lactamases
68 (BLaC). The addition of the BLaC inhibitor clavulanate suggests that beta-lactams combined with
69 BLaC inhibitors could be beneficial in the treatment of TB **(7).** Recent studies suggest that beta-
70 lactams, using clavulanate/clavulanic acid, show more activity against *M. tuberculosis***(7-14).**

71

The bacterial activity of beta-lactams is due to the inactivation of bacterial transpeptidases, commonly known as penicillin binding proteins (PBP), which inhibit the biosynthesis of the peptidoglycan layer of the cell wall of bacteria **(8,15).** Polymerizations of the peptidoglycan layer in most bacteria are predominantly cross-linked by D,D-transpeptidases (DDT), the enzymes inhibited by beta-lactams **(8,16)**. The majority of crosslinks in peptidoglycan appear to be formed by the non-classical L,D-transpeptidases (LDT) in *M. tuberculosis (***17-23).** Several studies revealed the structural basis and the inactivation mechanism of LDT and the active role of carbapenems, providing a basis for the potential use of carbapenems in inhibiting *M. tuberculosis* **(24-28).**

Beta-lactams show time-dependent activity, carbapenems have been shown to have bactericidal activity when the free drug plasma concentration exceeds the MIC for at least 40 % of the time in non-TB bacterial species **(29-30).**

Carbapenems are earmarked as potentially active drugs for the treatment of *M. tuberculosis*. To better understand the potential of carbapenems for the treatment of **M/XDR-**TB, the aim of this review was to evaluate the literature on currently available *in vitro*, *in vivo* and clinical data on carbapenems in the treatment of *M. tuberculosis* and detection of knowledge gaps, in order to target future research.

Methods

Prisma

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement **(31)**.

Search

In February 2018, a systematic literature search of PubMed and Web of Science, without restrictions with respect to publication date was employed using the key words (´Carbapenem' OR 'Carbapenems' OR 'Imipenem' OR 'Meropenem' OR 'Ertapenem' OR 'Doripenem' OR 'Faropenem' OR 'Biapenem' OR 'Panipenem' OR 'Tebipenem') AND ('Tuberculosis' OR TB OR Mycobacterium tuberculosis) as MeSh Terms. Retrieved studies and abstracts from both PubMed and Web of Science were pooled and duplicates were removed. Titles and abstracts of retrieved articles were screened. Reviews, case-reports or studies on other species than TB or studies on other drugs than carbapenems were excluded. Studies were screened for eligibility. If eligible, the full-text was read by a researcher (SvR). A second researcher (MZ) independently repeated the article search and selection. Discrepancies were resolved by discussion, or a third researcher was consulted (JWA). Full text papers were subdivided into three sections; *in vitro, in vivo* and clinical data. Full text papers for *in vitro* data were eligible for inclusion if an *M. tuberculosis* strain was studied and minimum inhibitory concentrations were reported. Full text papers for *in vivo* data were eligible for inclusion if treatment of *M. tuberculosis* infections with carbapenems were studied in animal models, and if colony forming units and/or survival data were reported. Full text papers for clinical data were eligible for inclusion if pharmacokinetics of carbapenems or safety or response to treatment measured as surrogate end points (sputum conversion) or clinical end points were studied and reported. References of all included articles were screened by hand. The same systematic search was performed using clinicaltrials.gov to find ongoing studies investigating carbapenems in TB patients (Feb 2018).

Data extraction

A researcher (SvR) performed data extraction first by using a structured data collection form. A second researcher (MZ) verified the data extraction independently. Data were subdivided into three sections; *in vitro*, *in vivo* and clinical data. Variables in the section '*in vitro*' included; *M. tuberculosis* strain, experimental methods, drug of interest. Minimal inhibitory concentration, minimal inhibitory concentration with clavulanic acid, minimal bactericidal concentration and colony forming units (CFU) were extracted from the included articles. For the section '*in vivo*' the following data were included; *M. tuberculosis* strain, mice, route of infection, drug of interest with or without clavulanic acid, dose, and treatment, colony forming units and survival rate, were retrieved from the included articles. For the clinical section, we extracted data from the included articles on type of study population, number of subjects, study design, drug of interest, and dosage. Sputum smear, sputum culture, treatment success, adverse events and interruption due to adverse events were noted as outcomes. AUC, Peak drug concentration (C_{max}), half-life ($t_{1/2}$), Distribution volume (Vd), and clearance were extracted. Possibility of pooling data from included data was assessed on data presentation.

Data quality

No validated tool for risk of bias assessment for *in vitro* studies, *in vivo* studies and pharmacokinetic studies was available. To be able to assess the quality of each study, we verified if each study reported on key-elements required for adequate data interpretation. If studies reported adequately on the key-elements, risk of bias was considered to be low. If studies had missing data or if procedures were not clear or not mentioned, risk of bias was considered to be high. The following key-elements were identified for *in vitro* studies; description of lab or clinical strains, minimal sample size of >10 strains, >3 concentrations tested per drug, MIC/CFU determined using the proportion method, evaluation endpoint of minimal inhibitory concentration (MIC 50 or MIC 90), evaluation of endpoint of minimal bactericidal concentration (MBC99) and CFU reduction, for *in vivo* studies;

143 description of laboratory or clinical strains, type of mice, route of administration of the drug, dose
144 and treatment duration, MIC/CFU determined using the proportion method, evaluation of endpoint
145 of CFU and survival rate and for clinical studies; for *human* studies; study design, patient population
146 (TB/MDR-TB; HIV co-infection), number of study participants, endpoints tested, defined as sputum
147 smear conversion, sputum culture conversion, treatment success, adverse events. The following
148 components were checked for pharmacokinetic studies: sample size, type of patients, type of assay,
149 number of plasma samples drawn per patient, sample handling, use of validated analytical methods
150 and method of AUC calculation.
151
152 **Results**
153 Based on the selection criteria, 250 articles were retrieved in PubMed and 260 in Web of Science.
154 After removal of 146 duplicates, 364 articles remained for screening. After screening of the title and
155 abstract, 46 articles remained for full text evaluation. Reasons for exclusion included; not available
156 (n=6), other drugs (n=2), no MIC (n=1), case-report (n=1), other (n=1). After this process, 35 relevant
157 articles were included in this study (Flow chart; Fig 1). Due to low number and high diversity of
158 strains, analytical methods and study designs, presence of biochemical instability of the drugs of
159 interest, the short half-life of drugs of interest in mice and the diversity in MIC determination, we did
160 not have enough data to perform a meta-analysis. Risk of bias of the included studies is shown in
161 table S1. Studies on clinicaltrials.gov are shown in S2.
162
163 **In vitro**
164 Results of the *in vitro* studies reporting on carbapenems are presented in table 1.
165
166 **Imipenem**
167 Susceptibility testing of imipenem, using various analytical methods against strain H37Rv, H37Ra,
168 Erdman and clinical isolates of *M. tuberculosis* showed a range of MIC's between 2 – 32 mg/ L

169 without clavulanic acid and a range of MIC's between 0.16 – 32 with clavulanic acid. **(8,32-37).** When
170 Imipenem was combined with clavulanate it showed a 4-16-fold lower MIC against the *M.*
171 *tuberculosis* H37Rv reference strain **(8,33-35).**
172
173 **Meropenem**
174 Multiple studies reported that meropenem in presence of clavulanate is active *in vitro* against clinical
175 and lab strains, H37Rv and H37Ra, of *M. tuberculosis*, showing MIC's ≤ 1 mg/L. *In vitro* studies
176 reporting susceptibility of meropenem of *M. tuberculosis* reference strain and clinical isolates
177 showed MIC values between 1 - 32 mg/L **(8,33-44).** Meropenem in combination with clavulanic acid
178 was shown to have a MIC between 0.063 – 32 mg/L **(33-35,38,43)** Meropenem in combination with
179 clavulanate killed the non-replicating ss18b strain of *M. tuberculosis* moderately and was shown to
180 have a MIC of 0.125 – 2.56 mg/L against *M. tuberculosis* H37Rv strains **(8,34-35,40).** A decrease of a
181 2 log10 CFUs over six days was reported in *M. tuberculosis*-infected murine macrophages **(40).**
182
183 **Ertapenem**
184 In clinical strains of *M. tuberculosis* the MIC of ertapenem, as single agent, was 16 mg/L and when
185 combined with clavulanate 4 mg/L (**33,35)**. Another study showed ertapenem was unstable
186 degrading faster than the doubling time of *M. tuberculosis* in the growth media used, suggesting
187 previous published MICs of ertapenem are likely to be falsely high **(45).** In a hollow fiber model with
188 supplementation of ertapenem in a broth microdilution test, ertapenem showed a MIC of 0.6 ml/L
189 **(46).** A 28-day exposure-response hollow fiber model of TB study tested 8 different doses of
190 ertapenem in combination with clavulanate and identified the ertapenem exposure associated with
191 optimal sterilizing effect for clinical use. Monte Carlo simulation with 10,000 MDR-TB patients
192 identified a susceptibility breakpoint MIC of 2 mg/L for an intravenous dose of 2 g once a day that
193 achieved or exceeded 40%T>MIC. **(46)**
194 **Faropenem**

Faropenem showed a 4-fold reduction when combined with clavulanic acid **(33,34),** resulting in a MIC range between 1 - 5 mg/L **(33-34, 47-49)** In a hollow fiber model, the optimal target exposure was identified to be associated with optimal efficacy in children with disseminated TB using Monte Carlo simulations; the predicted optimal oral dose was 30 mg/kg of Faropenem/medoximil 3-4 times daily. The exposure target for Faropenem/medoximil was 60% T_{free}>MIC **(50).**

Other carbapenems

Other carbapenems, such as doripenem, biapenem and tebipenem showed at least a 2-fold reduction in MIC when combined with clavulanic acid **(33,37,43,51).**

In vivo

Results of the *in vivo* studies reporting on carbapenems are presented in table 2.

Imipenem

The bacterial burden in imipenem-treated CD-1 female mice (twice daily (BID) 100 mg/kg), infected with *M. tuberculosis* strain H37Rv, was reduced by 1.8 log10 in splenic tissue and 1.2 log10 in lung tissue after 28 days, showing an anti-mycobacterial effect as well as improved survival in this mouse model **(52).** In another study Swiss mice, infected with *M. tuberculosis* strain H37Rv, were treated with a subcutaneous administration of 100-mg/kg imipenem in combination with clavulanate once a day to simulate a human equivalent dose. The CFU count after 28 days of treatment increased compared to the CFU count at start of treatment. There only was a significant difference in the imipenem-clavunlaate treated mice **(35).**

Meropenem

It has been reported that 300 mg/kg BID meropenem alone, and in combination with 50 mg/kg clavulanate both resulted in a significant, though modest reduction, in CFUs in lung and spleen

tissues in C57BL/6 mice **(40).** Veziris *et al.* reported a CFU increase compared to start of the treatment of meropenem when given as mono-therapy or in combination with clavulanate in a dose of 100 mg/kg, on CFUs, spleen weights, or lung lesions in Swiss mice **(35).** Meropenem in a dose of 300 mg/kg in combination with clavulanate, 75 mg/kg thrice-daily given to BALB/c mice showed marginal reduction in CFU counts in the acute model and no reduction in the chronic model **(34).** Meropenem, given subcutaneously 300 mg/kg three times a day, showed a CFU count reduction of 1.7 log in the lungs of TF3157 DHP-1 deficient mice. **(53)**

Ertapenem

In a murine TB model infected with H37Rv, a dose of 100 mg/kg once daily ertapenem as monotherapye or in combination with clavulanate had neither bactericidal nor bacteriostatic activity in lungs and spleens of TB-infected mice. Spleen weight and lung lesions remained similar compared to the untreated group of mice. There was an increase in CFUs compared to the CFUs at the start of the treatment **(35).**

Other Carbapenems

An oral dose of 500 mg/kg Faropenem medoxil, given three times daily, gave a reduction of 2 log CFU count in the lungs of TF3157 DHP-1 deficient mice **(53).** Neither *in vivo* nor clinical studies for other carbapenems as part of a multi-drug regimen against TB were retrieved.

Clinical studies

Results of the clinical studies reporting on carbapenems are presented in table 3.

Imipenem

Ten patients were treated with imipenem in combination with two or more other antimicrobial agents. It was reported that it was likely that 1g of imipenem (BID) contributed to sputum culture

conversion in these patients **(52).** A prospective study evaluated 1000 mg/day imipenem/clavulanate at a dose of once daily in 12 patients, 11 of these patients received linezolid-containing regimens. All patients showed sputum and culture conversion within 180 days. No adverse events were reported for imipenem/clavulanate **(54).** In a large observational study, the clinical outcomes of 84 patients, treated with 500 mg imipenem/clavulanate four times a day, were compared with results from 168 controls. The study showed that imipenem-containing regimens achieved comparable results compared to the imipenem sparing regimens, while success rates were similar to major international MDR-TB cohorts **(55).**

Meropenem

A regimen including meropenem-clavulanate given to 18 patients with severe pulmonary XDR-TB led to sputum culture conversion in 15 patients, of which 10 has successfully completed and five patients were considered cured according to WHO guidelines. Long-term safety was not a problem in this study as no adverse events were reported **(56-57).** The first study, that evaluated efficacy, safety and tolerability, was a case-control study in 37 patients, who received meropenem/clavulanate as part of a linezolid based multi-drug regimen. This is the first study that showed an added value of meropenem/clavulanate in a multi-drug regimen. The meropenem/clavulanate containing regimen showed a sputum microscopy conversion of 87.5 % and a sputum culture conversion of 83.8%, while the meropenem/clavulanate sparing regimen showed a sputum microscopy conversion of 56.3% and a sputum culture conversion of 62.5% after 90 days of treatment **(58).** In another study, 10 XDR and pre-XDR female patients were treated with multi-drug regimens and received meropenem/clavunlanate for 6 months or more. Eight patients achieved sputum conversion after 6 months, while two patients died. **(59).** Pharmacokinetic parameters of 1 g meropenem/clavulanate given intravenously over 5 minutes showed a serum peak of 112 mg/ml and a concentration of 28.6 mg*h/L **(39).** In an observational retrospective cohort-study, efficacy and safety were evaluated in 96 patients treated with meropenem/clavulanate containing regimens and compared with 168 controls.

Sputum smear and culture conversion rates were found to be similar **(60)** In an observational study comparing therapeutic contribution, such as sputum smear and culture conversion rates and success rates, of imipenem/clavulanate and meropenem/ clavulanate in a background regimen, suggested that meropenem/clavulanate can contribute to the efficacy of a regimen in treating M/XDR-TB patients **(11).**

Ertapenem

The first report on clinical experience with ertapenem presented data from five patients who were treated with an intravenous injection of 1 g ertapenem once daily in a multi-drug regimen. Three of these patients showed sputum smear and culture conversion; four of five patients had a successful treatment outcome. Two patients interruped treatment due to an adverse event. These adverse events were considered unrelated to the study drug **(61).** In an observational study 18 patients were treated with 1 g ertapenem once daily; fifteen of these patients had a successful treatment outcome were cured. Three patients were lost due to follow-up. Three patients stopped ertapenem treatment due to ertapenem unrelated adverse events. Pharmacokinetic parameters were evaluated in 12 patients, showing a mean peak plasma of 127.5 (range 73.9 - 277.9) mg /L and an AUC of 544.9 (range 390 - 1130) mg*h/L. Based on a MIC of 0.25 mg/ml 11/12 patients reached the target value of 40% T_{free}>MIC was exceeded **(10).** The pharmacokinetic model composed in this study was shown to adequately predict ertapenem exposure in MDR-TB patients. The Monte Carlo simulation, which had a time restriction of 0–6 h, showed that the best performing limited sampling strategy was at 1 and 5 h after intravenous injection. **(62).** In another pharmacokinetic model study using prospective data from 12 TB patients it was observed that 2 g ertapenem once daily resulted in a more than a dose-proportional increase in AUC compared to once daily 1 g ertapenem. Based on a MIC of 1.0 mg/L, 11 out of 12 patients reached the target value of 40% T_{free}>MIC **(63).**

Discussion

Hugonnet and colleagues first stated that carbapenems have antimycobacterial activity **(7).** Subsequently, studies addressing the inactivation mechanism of LDT provided the underlying evidence to support the hypothesis of activity of carbapenems against *M. tuberculosis* **(14-28).** In spite of this a series of *in vitro* studies have been carried out, some of which detected an effect and some of which did not **(8,32-50).** Only later, was it recognized that these confusing results are probably explained by the chemical instability of carbapenems, in culture media at the temperatures typically used in *in vitro* studies, and many previously published *in vitro* studies are likely to have reported falsely high MICs **(45).**

Overall the results of the studies identified in this review, which used a variety of experimental methods to test clinical and laboratory strains of *M. tuberculosis* for susceptibility to carbapenems, are consistent. Carbapenems are more active against *M. tuberculosis* if used in combination with clavulanate, a BLaC inhibitor. **(8,32-50)**. In line with these *in vitro* studies the addition of clavulanate improved the survival rate in mice (**35).** As the European Medicines Agency (EMA) has accepted and qualified the *in vitro* hollow fiber system models as a methodology to define pharmacokinetic and pharmacodynamic (PK/PD) parameters, these modern *in vitro* studies can be used to avoid the problems associated with the chemical instability of these agents in standard agar based MIC testing. Thus, hollow fiber systems have the potential for dose finding and regimen selection studies on the use of carbapenems in the treatment of TB **(64-65)**.

Few *in vivo* studies have been performed due to the short half-life and lower serum concentrations of carbapenems in mice **(35)**.

One prospective, two observational and seven retrospective clinical studies to assess effectiveness, safety and tolerability of three different carbapenems (imipenem, meropenem and ertapenem) have been performed. Adverse events due to carbapenems were mild, confirming what we know from other infectious diseases; but in contrast to other repurposed drugs like linezolid **(55,58,60).** To date,

only two large retrospective studies with M/XDR-TB patients have been performed with imipenem (84 patients), and meropenem (96 patients) **(11).** Meropenem/ clavulanate was suggested to be more efficient in managing M/XDR-TB **(11)**, however interpretational limitations were mentioned.

We found no clear evidence to select one particular carbapenem among the different candidate compounds, when designing an effective M/XDR-TB regimen. Both economical and clinical factors play a role. Whereas imipenem is the cheaper carbapenem, ertapenem has the potential advantage that it is only given once daily; and meropenem is by some authors believed to be the most effective in humans, but no head-to-head comparison studies have confirmed this to date. Therefore, more clinical evidence and dose optimization substantiated for example by hollow fiber infection studies are needed to support the repurposing carbapenems for the treatment of M/XDR-TB.

Clinical studies are hampered by the fact that currently no combination of a carbapenem with clavulanate is commercially available. Furthermore, clavulanate is not available alone so at present it is not practically possible to prescribe carbapenem with clavulanate. Therefore, amoxicillin – clavulanate is often co-administered along with a carbapenem in case the latter is preferred for treatment. Unfortunately, amoxicillin has gastrointestinal side effects potentially complicating prolonged treatment. Therefore, combined treatment amoxicillin– clavulanate with a carbapenem is only an option for TB treatment of complicated cases showing multi- or extensive drug resistance **(42).** Although, Gonzalo *et al.* reported a potential benefit that MIC values drop when amoxicillin is added to a combination of meropenem and clavulanate.

Due to different procedures, analytical methods and design, the biochemical instability of the drugs of interest, the short half-live of drugs of interest in mice, diversity in MIC determination and intolerance in addition to resistance, it was not possible to perform a meta-analysis. While the observational data are promising, carbapenems can only recommended in case of resistance to group A and group B drugs in M/XDR-TB treatment.

The ideal carbapenem would have the antimycobacterial activity of imipenem, the half-life of ertapenem and the oral bioavailability of tebipenem-pivoxil. Due to increasing resistance observed in XDR-TB isolates **(66-67)** and in MDR-TB patients with resistance to an aminoglycoside, carbapenems may be a valuable alternative to the current injectable second line drugs. Assessment of intracellular activity as well as activity against dormant *M. tuberculosis* by carbapenems is a critical step to further explore the potential of these repurposed drugs.

As successful treatment outcome for M/XDR-TB is still poor, ranging from 25-50% **(1)** an improvement of the current treatment is urgently needed. An individual data meta-analysis among 12,030 individual patients from 50 studies showed a significantly better treatment outcome for patients who received carbapenems compared to other drugs traditionally used for treatment of MDR-TB. **(68)**. Since there is a need for new or repurposed drugs for the treatment of M/XDR-TB, phase II/ III clinical trials are urgently needed for carbapenems to further evaluate their potential. Long term safety and activity against *M. tuberculosis* are supported by observational data and several studies **(41,50,69).** A phase II prospective randomized controlled study evaluating a carbapenem plus a BLaC inhibitor on top of an optimized background regimen versus standard of care would be an appropriate strategy to test the potential benefits of carbapenems for M/XDR-TB treatment.

Conclusion

Now the variable results of *in vitro* studies have been explained and the activity of carbapenems in the presence of a BLaC inhibitor is established, these drugs should be further developed for the treatment of multi- and extensive drug resistant *M. tuberculosis*. Ultimately, a well-designed phase 2 study is needed to substantiate the claimed benefits of carbapenems in patients with drug-resistant TB.

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639 Figure 1: Flow chart

640 Table 1: Results of the *in vitro* studies reporting on carbapenems
641 N: number of strains, MIC: Minimal inhibitory concentration (mg/L), MIC50: Minimal inhibitory
642 concentration required to inhibit growth of 50% of the organisms, MIC90: Minimal inhibitory
643 concentration required to inhibit growth of 90% of the organisms, CLV: clavulanate (mg/L) , MBC99:
644 minimal bactericidal concentration that kills 99% of replication culture (mg/L), CFU: colony forming
645 units (Log/(CFU/ml))

646 Table 2: Results of the *in vivo* studies reporting on carbapenems
647 MIC: Minimal inhibitory concentration (mg/L) , CLV: clavulanate (mg/L) , MBC: minimal bactericidal
648 concetration (mg/L), CFU: colony forming units. qd: once a day, bid: twice a day, tid: three times a
649 dat, qid: four times a day, ND: not described.

650
651 Table 3: Results of the *in human* studies reporting on carbapenems
652 qd: once a day, bid: twice a day, tid: three times a dat, qid: four times a day. PK: pharmacokinetic,
653 ND: not described

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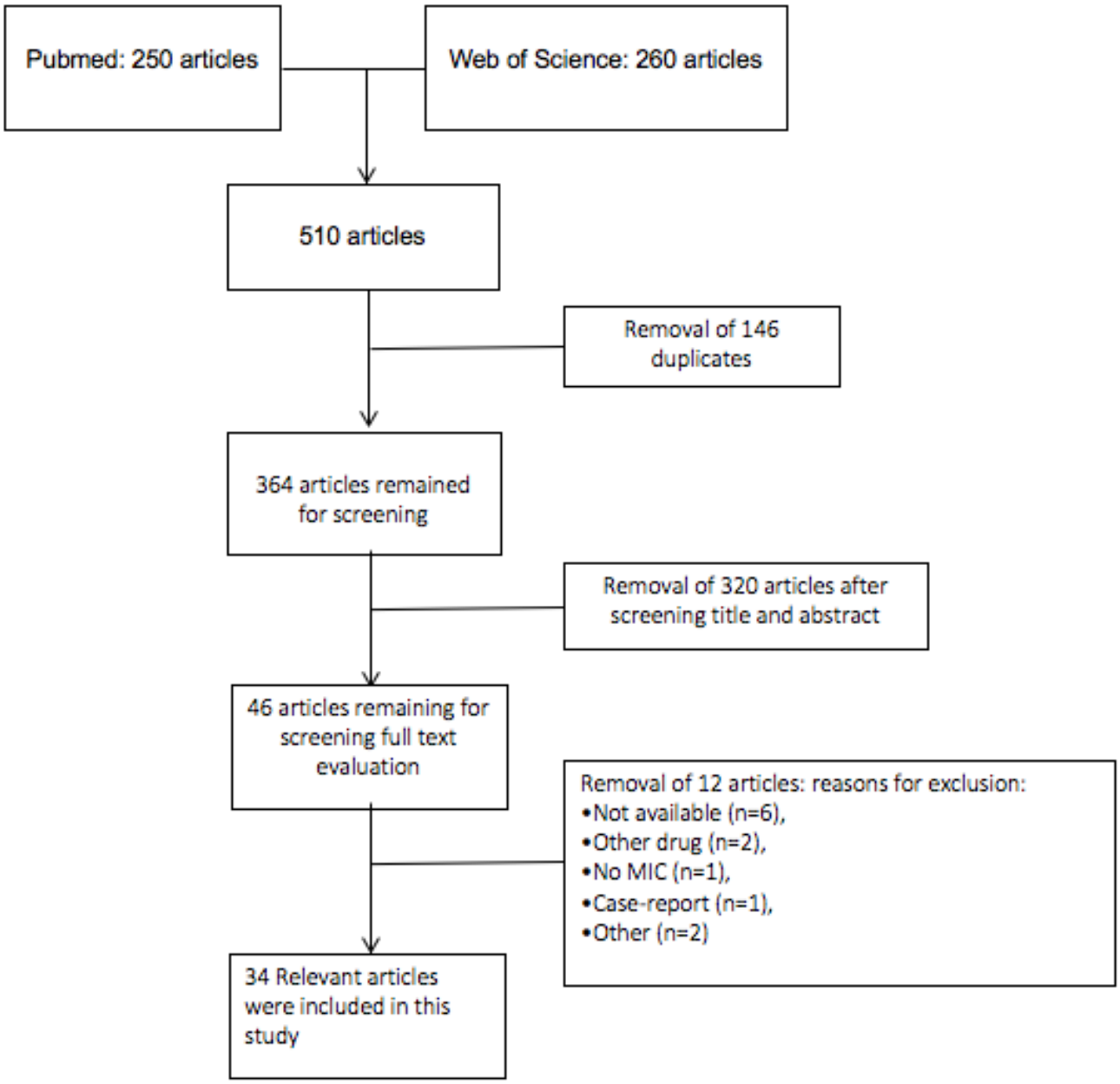

First author (ref).	Strain	N	Method	Carbapenem	Betalactamase inhibitor	MIC	MIC50	MIC90	MIC/CLV	MIC50/CLV	MIC90/CLV	MBC99	Δ log CFU reduction
Chambers et al (32)	H37Ra, H37Rv, clinical isolates	7	Bactec TB system	Imipenem	None	(2-4)							
Cohen et al (38)	H37Rv, Clinical isolates	91	Microplate alamar Blue assay	Meropenem	Clavunalate	22 (2-32)			5,4 (0,5 - 32)				
Cavanaugh et al (39)	Clinical isolates	153	Resazurin microdilution assay	Meropenem	Clavunalate				(<0,12 - >16)	1	8		
Deshpande et al (47)	H37Ra, THP 1 monocytes	1	Resazurin microdilution assay, CFU counts	Faropenem	None	1							2.71 log
Dhar et al (49)	H37Rv, Erdman	2	96 Well flat-bottom polystyrene microtiter plate	Faropenem Meropenem Imipenem	Clavunalate	1,3 2,5 2,5			1,3 0,3 0,5				
England et al (40)	H37Rv, macrophages	1	CFU counts	Meropenem	Clavunalate								2 log
Forsman et al (41)	H37Rv, Clinical isolates	69	Broth microdilution	Meropenem	Clavunalate				(0.125-32)		1		
Gonzalo et al (42)	H37Rv, Clinical isolates	28	960 MGIT system	Meropenem	Clavunalate	resistant at 5 mg/L			(1.28 - 2.56)				
Gurumurthy et al (48)	H37Rv	1	96 Wells plate	Faropenem	None			5-10				20	0 log

Horita et al (43)	H37Rv, Clinical isolates	42	Broth microdilution	Meropenem Biapenem Tebipenem	Clavunalate (Avibactam)	1-32 1-32 0.25-8	16 16 4	32 32 8	0.063-8 0.25-8 0.063-8	2 2 1	4 4 1		

Table 1: Results of the *in vitro* studies reporting on carbapenems

Hugonnet et al (8)	Erdman, H37Rv, Clinical isolates	15	Broth microdilution	Imipenem Meropenem	Clavunalate				0.16 0.23-1.25				
Kaushik et al (33)	H37Rv, Clinical isolates	1	Broth microdilution	Imipenem Meropenem Ertapenem Doripenem Biapenem Faropenem Tebipenem Panipenem	Clavunalate			40-80 5-10 10-20 2.5-5 2.5-5 2.5-5 1.25-2.5 >80			20-40 2.5-5 5-10 1.25-2.5 0.6-1.2 2.5-5 0.31-0.62 ND	ND 80 ND 20 20 20 10 ND	
Kaushik et al (51)	H37Rv, strain 115R, strain 124R	3	Broth microdilution	Biapenem	None	(2-8)							
Sala et al (44)	18b cells	1	Serial dilutions, CFU counts	Meropenem	Clavunalate								2 log
Solapure et al (34)	H37Rv, 18b cells	1	Resazurin microdilution assay, CFU counts	Imipenem Meropenem Faropenem	Clavunalate	4 8 4			0.5 1 2			4 (5 mg/ml) 2 (4	
Srivastava et al (45)	H37Ra	1	Resazurin microdilution assay	Ertapenem	Clavunalate	0.6							2.38 log10
Veziris et al (35)	H37Rv	1	Broth microdilution	Imipenem Meropenem Ertapenem	Clavunalate		16 8 16			1 1 4			

Table 2: Results of the *in vivo* studies reporting on carbapenems

First author (ref).	Strain	Mice	Infection	Drug	Dose	Infection model	Treatment	End-point	Organs	CFU reduction	Survival rate	CFU/ clv
Chambers et al (52)	H37Rv	CD-1 Female mice	subcutaneously	Imipenem	Bid 100 mg/kg	ND	28 days	CFU count, Survival rate	Spleen, lungs	1.8 log	65%	ND
Dhar et al (49)	H37Rv	adult C57BL/6J mice	intratracheal	Faropenem	500 mg/kg	acute TB	8 days	CFU count	Lungs	reduction of CFU: 10^5 - 10^6	ND	ND
England et al (40)	H37Rv	C57BL/6 Mice	subcutaneously	Meropenem	bid 300 mg/kg	Chronic stage	2 weeks	CFU count	Spleen, lungs	1 log	ND	1 log
		New zealand white rabbits	intravenous bolus	Meropenem	75 mg/kg 125 mg/kg	ND	ND	PK data	ND	ND	ND	ND
Kaushik et al (51)	H37Rv	BALB/c mice	Aerosol	Biapenem	200 mg/kg BID 300 mg/kg BID	Late phase acute TB rifampicin resistant TB	8 weeks 4 weeks	CFU count	Lungs	1 log ND	ND	ND
Rullas et al (53)	H37Rv	TF3157 DHP-I KO	subcutaneously	Meropenem Faropenem	TID 300 mg/kg TID 500 mg/kg	Acute TB model	21 days	CFU count	Lungs	1.7 log 2 log	ND ND	ND ND
Solapure et al (34)	H37Rv	BALB/c mice	Aerosol	Meropenem	TID 300 mg/kg	Acute and chronic model	4 weeks	CFU count	lungs	no reduction	ND	no reduction
Veziris et al (35)	H37Rv	Female Swiss mice	Intravenously	Imipenem Meropenem Ertapenem	100 mg/kg 100 mg/kg 100 mg/kg	preventive model	28 days	CFU count, Survival rate	Spleen, lungs	>1.2 log* >1.8 log* >1.7 log*	1 dead 3 dead 3 dead	>0.9 log* >1.4 log* >1.6 log*

Table 3: Results of the *in human* studies reporting on carbapenems

First author (ref)	year of publication	Country	Study population	Study design	Drug	Dosage	Patients	Paediatric	Sputum Smear	Sputum culture	Treatment succes	Adverse events	interruption due AE
Arbex et al (54)	2016	Brazil	2013 - 2015	Observational, retrospective	Imipenem	1 g oc	12	No	12/12	12/12	7/12	0/12	0/12
Chambers et al (52)	2005	USA	ND	Prospective	Imipenem	1 g bid	10	No	ND	8/10	7/10	ND	ND
De Lorenzo et al (58)	2014	Italy, The Netherlands	2001-2012	Observational case-control	Meropenem	1 g tid	37	No	28/32	31/37	ND	5/37	2/5
Payen et al (57)	2018	Belgium	2009-2016	Retrospective case series	Meropenem	2 g tid (then bid)	18	No	16/18	16/18	15/18	0/18	0/18
Palmero et al (59)	2015	Argentina	2012-2013	Retrospective	Meropenem	2 g tid (then 1 g tid)	10	No	ND	8/10	3/6	0/10	ND
Van Rijn et al (10)	2016	The Netherlands	2010-2013	Retrospective	Ertapenem	1 g oc	18	yes	ND	15/18	15/18	2/18	3/18
Tiberi et al (61)	2016	Italy, The Netherlands	2008-2015	Retrospective, cohort	Ertapenem	1 g oc	5	No	3/5	3/5	4/5	0/5	0/5
Tiberi et al (60)	2016	Italy, The Netherlands	2003-2015	Observational, retrospective, cohort	Meropenem	1 g tid (2g tid)	96	No	55/58	55/58	55/96	6/93	8/94

Tiberi et al (11, 55)	2016	-	2003-2015	Observational retrospective case-control	Imipenem	500 mg qid	84	No	51/64	51/64	34/57	3/56	4/55